Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Middleton PG, Mall MA, Dřevínek P, et al. Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele. N Engl J Med 2019;381:1809-19. DOI: 10.1056/NEJMoa1908639

Supplementary Appendix to:

ELEXACAFTOR-TEZACAFTOR-IVACAFTOR FOR CF WITH A SINGLE *PHE508DEL* MUTATION

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Supplementary Methods

Primary Endpoint: Global and European Protocol Versions

The primary endpoint of the global protocol was the absolute change in percentage of predicted forced expiratory volume in 1 second (FEV_1) from baseline at week 4, with the first key secondary endpoint being the absolute change from baseline in percentage of predicted FEV_1 through week 24. At the request of European regulators, in the European protocol, the primary endpoint was the absolute change from baseline in percentage of predicted FEV_1 through week 24 and the first key secondary endpoint was the absolute change from baseline in percentage of predicted FEV_1 at week 4. The other key secondary endpoints were the same in the global and European protocols.

Inclusion Criteria

- Patient (or legal guardian) signed and dated the informed consent form
- Willing and able to comply with study requirements and restrictions
- 12 years of age or older
- Diagnosis of cystic fibrosis
- *Phe508del*/minimal function genotype (see below for minimal function definition and Table S1 for qualifying mutations)[1]
- Percentage of predicted FEV_1 ≥40 and ≤90 at screening
- Stable cystic fibrosis disease as judged by the investigator
- Willing to remain on a stable cystic fibrosis treatment regimen

Exclusion Criteria

- History of any illness or clinical condition that in the opinion of the investigator might confound the study results or pose an additional risk in administering study drug(s) to the patient. This includes, but is not limited to, the following:
    - Clinically significant cirrhosis with or without portal hypertension
    - Solid organ or hematological transplantation

    - Alcohol or drug abuse in the past year, including, but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator
    - Cancer, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (all 3 with no recurrence for the last 5 years)
- Any of the following abnormal laboratory values at screening:
    - Hemoglobin <10 g/dL
    - Total bilirubin ≥2 × upper limit of normal (ULN)
    - Aspartate aminotransferase, alanine aminotransferase, ɣ-glutamyl transferase, or alkaline phosphatase ≥3 × ULN
    - Abnormal renal function defined as glomerular filtration rate ≤50 mL/min/1.73 m^2 (calculated by the Modification of Diet in Renal Disease Study Equation) for patients ≥18 years of age and ≤45 mL/min/1.73 m^2 (calculated by the Counahan-Barratt equation) for patients aged 12 to 17 years (inclusive)
- An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for sinopulmonary disease within 28 days before the first dose of study drug (Day 1)
- Lung infection with organisms associated with a more rapid decline in pulmonary status (including, but not limited to, *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*)
- An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug (Day 1)
- Ongoing or prior participation in a study of an investigational treatment within 28 days or 5 terminal half-lives (whichever is longer) before screening. The duration of the elapsed time may be longer if required by local regulations
- Use of prohibited medications as defined in the study protocol, within the protocol-specified window before the first dose of study drug (Day 1)
- Pregnant or nursing females. Females of childbearing potential must have a negative pregnancy test at screening (serum test) and Day 1 (urine test)

- The patient or a close relative of the patient is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site

Definition of Minimal Function Mutation

Minimal function mutations were defined in the protocol as the subset of *CFTR* mutations that are nonresponsive to ivacaftor and tezacaftor/ivacaftor and meet at least 1 of the following criteria: (1) no biological plausibility of translated protein (genetic sequence predicts the complete absence of CFTR protein) or (2) in vitro testing that supports lack of responsiveness to tezacaftor, ivacaftor, or tezacaftor/ivacaftor and provides evidence of clinical severity on a population basis (as reported in large patient registries). Mutations considered to be minimal function mutations based on in vitro testing met the following criteria in in vitro experiments: (1) baseline chloride transport that was <10% of wild-type CFTR and (2) an increase in chloride transport of <10% over baseline following the addition of tezacaftor, ivacaftor, or tezacaftor/ivacaftor in the assay. Patients with these mutations on one allele and *F508del* on the other allele exhibited evidence of clinical severity defined as (1) average sweat chloride >86 mmol/L and (2) prevalence of pancreatic insufficiency >50%. **Table S1** lists minimal function mutations detectable by a US Food and Drug Administration–cleared genotyping assay or other method that were stated in the protocol as meeting the eligibility criterion; however, the protocol list was not intended to be exhaustive, and the protocol instructed investigators to contact the medical monitor regarding other mutations that might also meet the eligibility criterion.

Spirometry

Spirometry was performed according to American Thoracic Society and European Respiratory Society criteria,[2] and values were expressed as percentage of predicted values using the Global Lung Function Initiative reference equations.[3]

CF-Related Care

Clinical care of participating patients was managed by the site investigators. Patients were instructed to remain on a stable treatment regimen for their cystic fibrosis from 28 days before the Day 1 Visit through completion of study participation. “Stable treatment regimen” was defined as the current treatment regimen for cystic fibrosis that patients had been following for at least 28 days before the Day 1 Visit. Patients were asked not to initiate long-term treatment with new medication from 28 days before the Day 1 Visit through completion of study participation. Patients who were taking inhaled tobramycin or other chronically inhaled antibiotics were advised to remain on that regimen throughout the study. The protocol included specific guidance regarding use of CYP3A inducers (including glucocorticoids and ciprofloxacin), CYP3A inhibitors, and OATP1B1 substrates. It also included guidance on when to interrupt study drug administration, and when to discontinue study drug altogether.

Statistical Analysis

Planned Interim Analysis of Primary Endpoint: Absolute Change From Baseline in Percentage of Predicted FEV_1 at Week 4 (global protocol)

An interim analysis was planned to occur after at least 140 patients completed the week 4 visit and at least 100 patients completed the week 12 visit. A Lan and DeMets α-spending function was applied to control the overall type I error rate of 0.05 for the primary endpoint of absolute change from baseline in percentage of predicted FEV_1 at week 4. Based on the planned sample size for interim analysis, the primary endpoint was to be tested at an α of 0.044 at the interim analysis while also preserving an α of 0.01 for the final analysis in case statistical significance was not attained at the interim analysis.

Due to rapid enrollment in this study, all patients were included in the interim analysis because the interim analysis took place at least 4 weeks after the last patient received their first dose of study drug. As a result, the endpoint of absolute change in percentage

of predicted FEV_1 at week 4 was tested at the full α of 0.05 for the interim analysis. No secondary endpoints were tested for statistical significance during the interim analysis.

The interim analysis was performed by an external independent biostatistician who was not involved in the study, and the results were reviewed by the independent data monitoring committee. After the interim analysis, the study continued to completion and remained double-blinded through week 24, apart from the planned unblinding of a limited Vertex team that was tasked with preparing regulatory submissions. To protect study integrity, members of the limited Vertex unblinded team were not involved in and did not influence the ongoing conduct of the study.

The final analysis was performed after all subjects completed their study participation. All key secondary endpoints were tested at the final analysis.

Analysis of Number of Pulmonary Exacerbations Through Week 24 as a Key Secondary Endpoint

As part of the final analysis of the key secondary endpoints, the number of pulmonary exacerbations through week 24 was assessed. This assessment used a negative binomial regression model with a fixed effect for treatment, and continuous baseline percentage of predicted FEV_1, age at screening (<18 years vs ≥18 years), and sex (female vs male) as covariates; the logarithm of patient-specific analysis period duration was included in the model as an offset.

A pulmonary exacerbation was defined as a new event or change in antibiotic therapy (intravenous, inhaled, or oral) for any 4 or more of the following signs/symptoms[4]:

- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea

- Malaise, fatigue, or lethargy
- Temperature above 38°C (equivalent to approximately 100.4°F)
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical examination of the chest
- Decrease in pulmonary function by 10%
- Radiographic changes indicative of pulmonary infection

Sample Size and Power for Number of Pulmonary Exacerbations through Week 24

Assuming a pulmonary exacerbation rate of 0.6 over 24 weeks for the placebo group, an overdispersion parameter of 0.5 in each treatment group and a 10% dropout rate, the planned overall sample size of 180 patients per treatment group provided approximately 80% power to detect a 40% reduction in the pulmonary exacerbation rate with triple combination therapy as compared to placebo based on a 2-sided, 2-sample negative binomial regression model test for the ratio of rates, at a significance level of 0.05.

Additional Analysis of Percentage of Predicted FEV_1 and Sweat Chloride

In addition to the pre-specified analyses of the absolute change from baseline in percentage of predicted FEV_1 and sweat chloride using a mixed-effects model for repeated measures, the baseline and post-baseline values were summarized using descriptive statistics including mean, standard error and 95% CI.

Multiplicity Adjustment for Analysis of Key Secondary Endpoints

The analysis plan specified that the key secondary endpoints would be formally tested at the final analysis if the primary endpoint was statistically significant. A hierarchical testing procedure was used to control the type I error rate for the multiple key secondary

endpoints tested at an α of 0.05. For a test to be considered statistically significant within the testing hierarchy, all preceding tests within the hierarchy must be statistically significant at the 0.05 level. The testing order of the key secondary endpoints in the global protocol was:

- Absolute change from baseline in percentage of predicted FEV_1 through week 24
- Number of pulmonary exacerbations through week 24
- Absolute change from baseline in sweat chloride through week 24
- Absolute change from baseline in Cystic Fibrosis Questionnaire–Revised respiratory domain score through week 24
- Absolute change from baseline in body mass index at week 24
- Absolute change from baseline in sweat chloride at week 4
- Absolute change from baseline in Cystic Fibrosis Questionnaire–Revised respiratory domain score at week 4

Analysis of Safety Data

Safety analyses included all patients who received ≥1 dose of elexacaftor-tezacaftor-ivacaftor or placebo. These analyses were based on data from the period from the first dose of study drug to the earlier of the following: (1) 28 days after the last dose of study drug or (2) the date of completion of study participation. Two patients who were randomized to the placebo arm took at least one dose of elexacaftor-tezacaftor-ivacaftor or ivacaftor due to a study drug dispensation error; these two patients were summarized in the active arm per the statistical analysis plan.

Handling of Missing Data

The mixed model for repeated measures approach used for analysis of efficacy endpoints provides unbiased results under the assumption that data are missing at random; consequently, no imputation of missing data was performed. In addition, a sensitivity analysis based on multiple imputation confirmed that the results for the primary endpoint as well as the key secondary endpoint pertaining to percentage of predicted FEV_1, was unaffected by missing data. For safety analysis, missing and

partial adverse event start dates were imputed using a conservative approach to determine whether these events were treatment emergent.

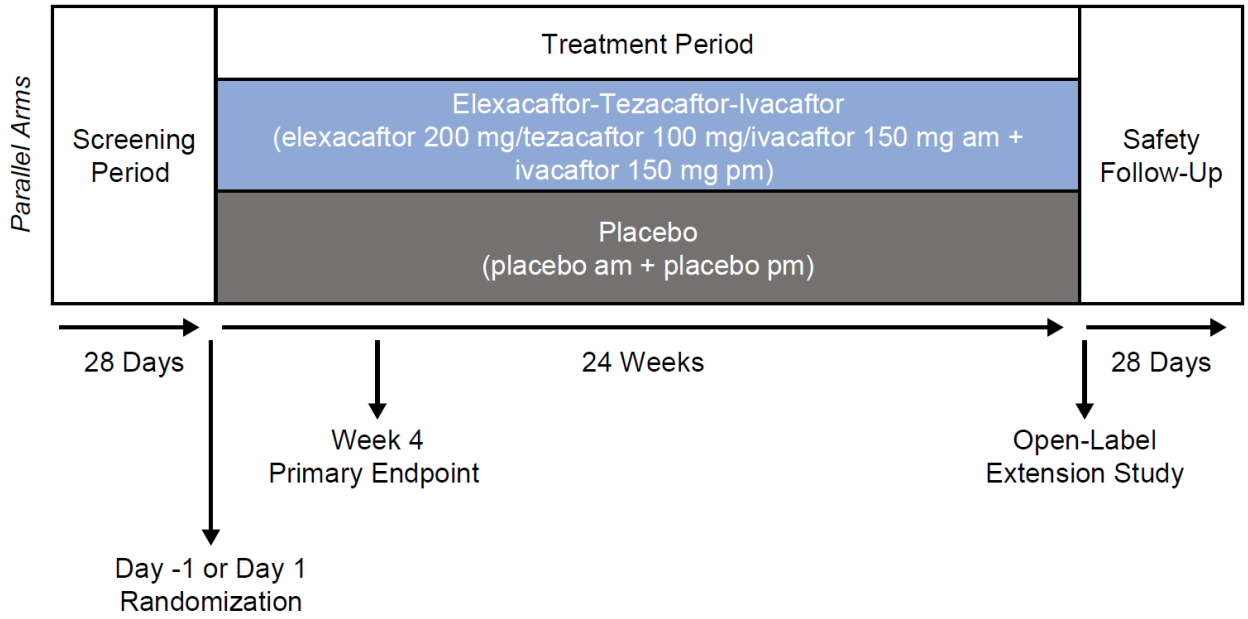
Supplementary Results

Compliance with Study Drug Regimen

Compliance, defined as the number of days the patient took study drug divided by the number of days from the first dose of study drug to the last dose of study drug, had a mean value of 98.8% in the elexacaftor-tezacaftor-ivacaftor group and 99.6% in the placebo group.

Supplementary Methods

Figure S1. Study Design.



Supplementary Results

Figure S2. CONSORT Diagram.

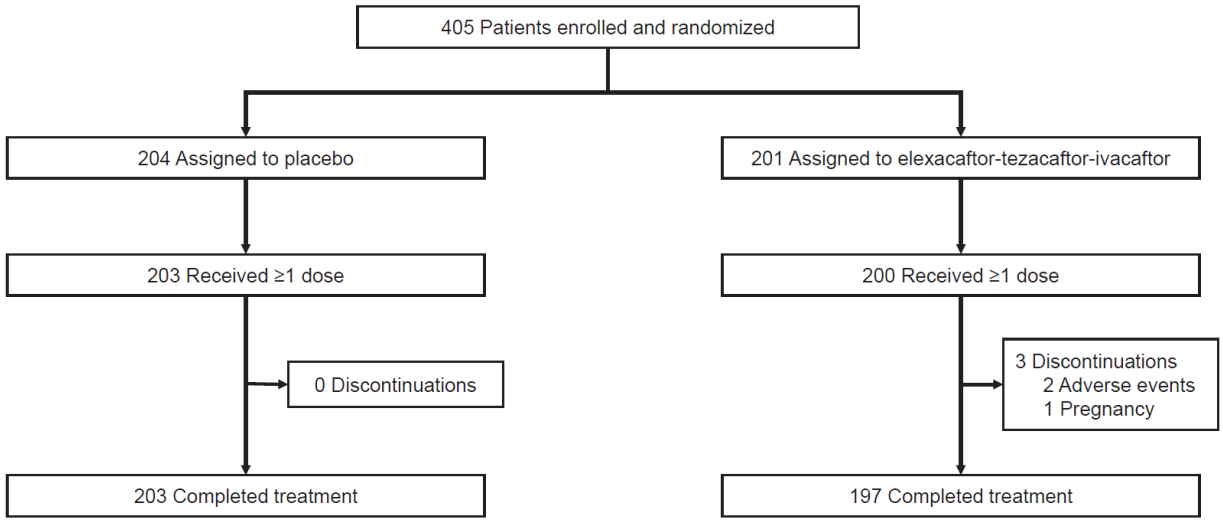
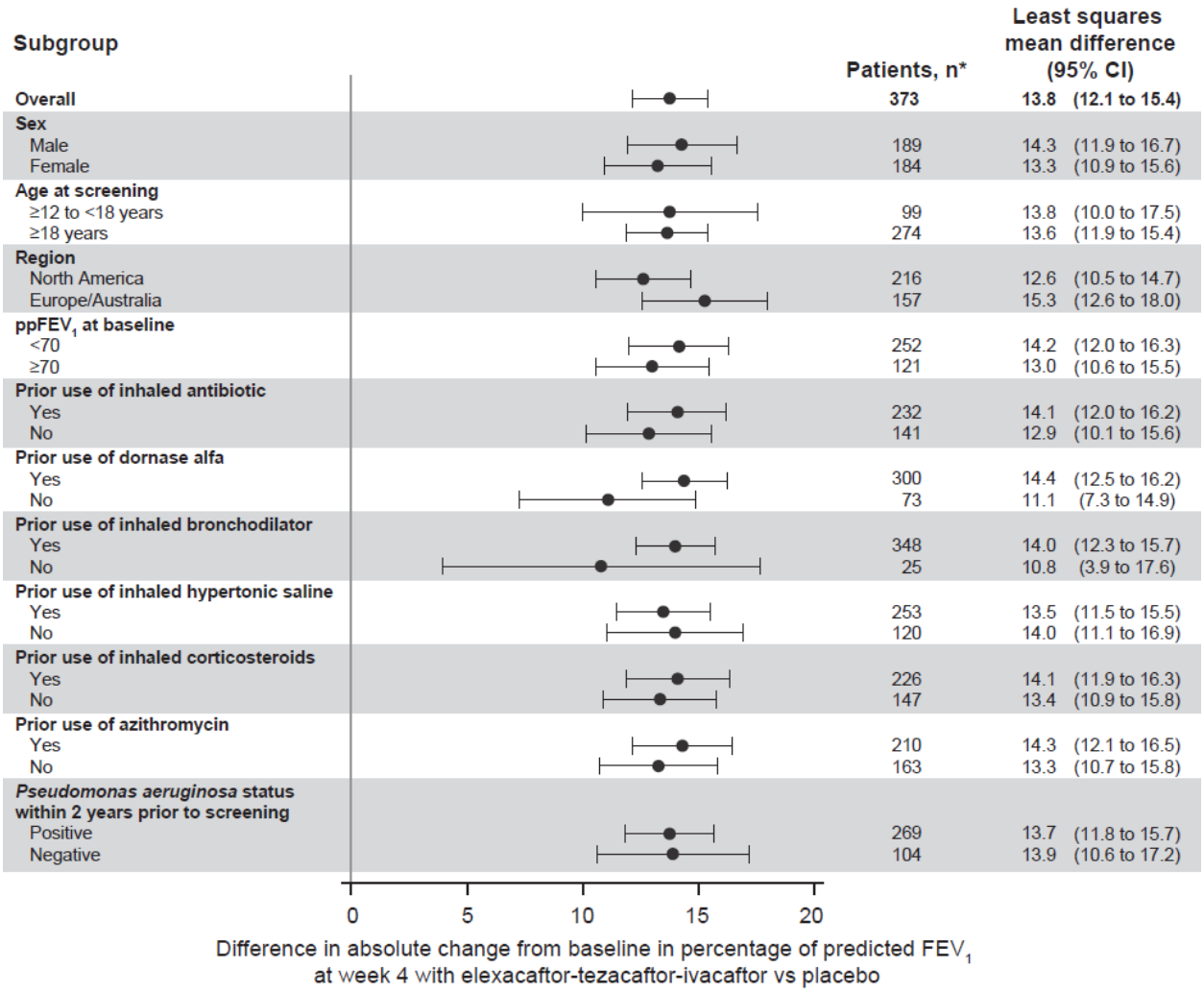
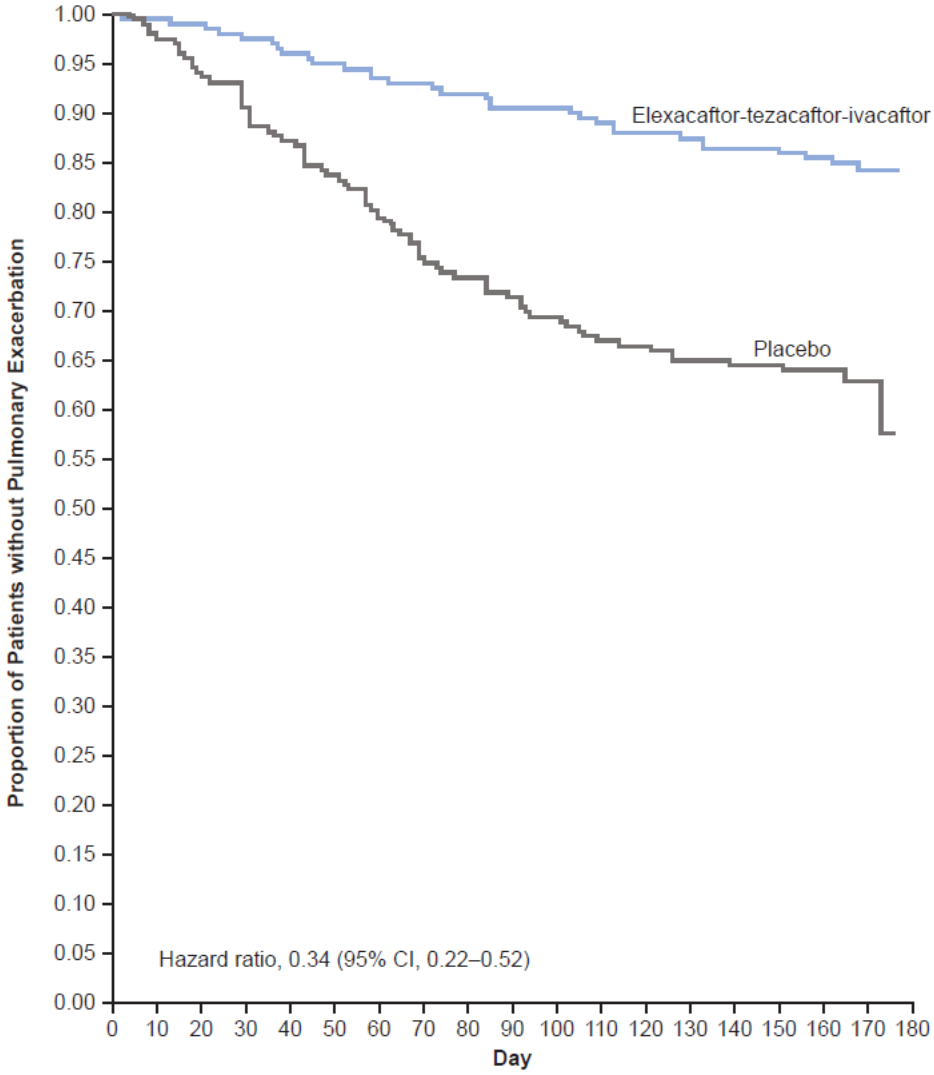


Figure S3. Absolute Change From Baseline in Percentage of Predicted FEV_1 at Week 4 in Pre-specified Subgroups.



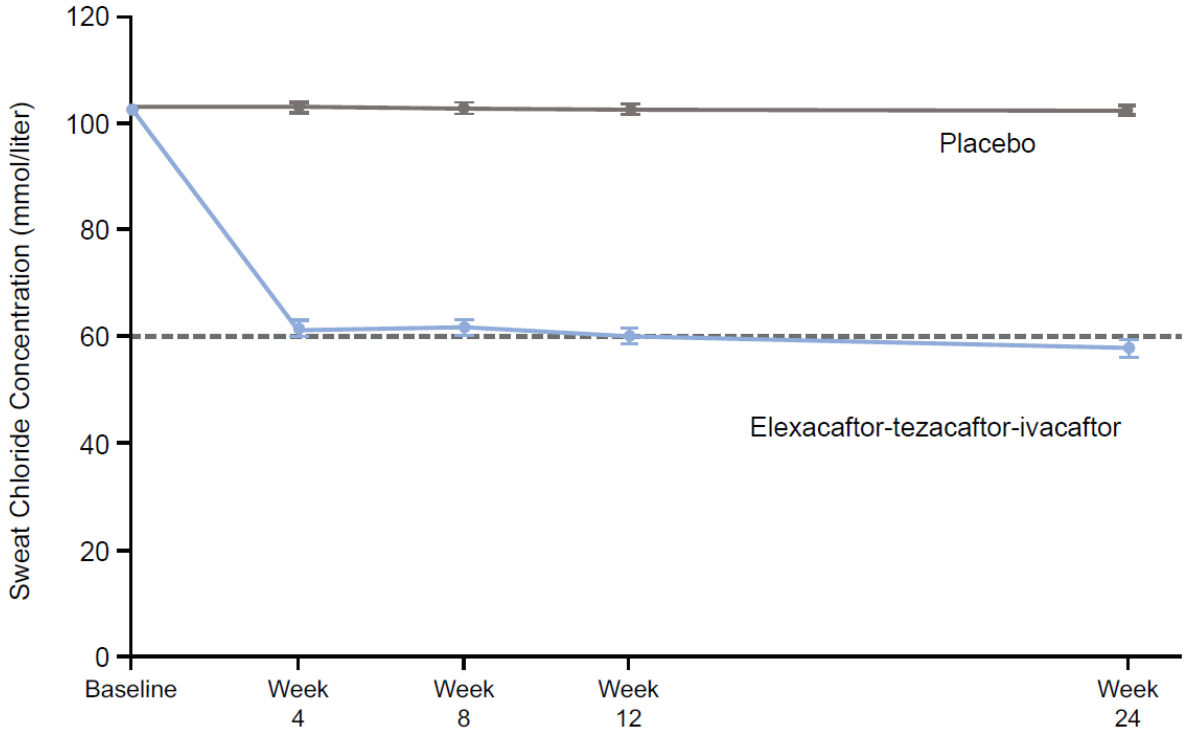
* Listed n values indicate the number of patients in the pre-specified subgroup who have non-missing FEV_1 data at week 4.

Figure S4. Time-to-First Pulmonary Exacerbation.*



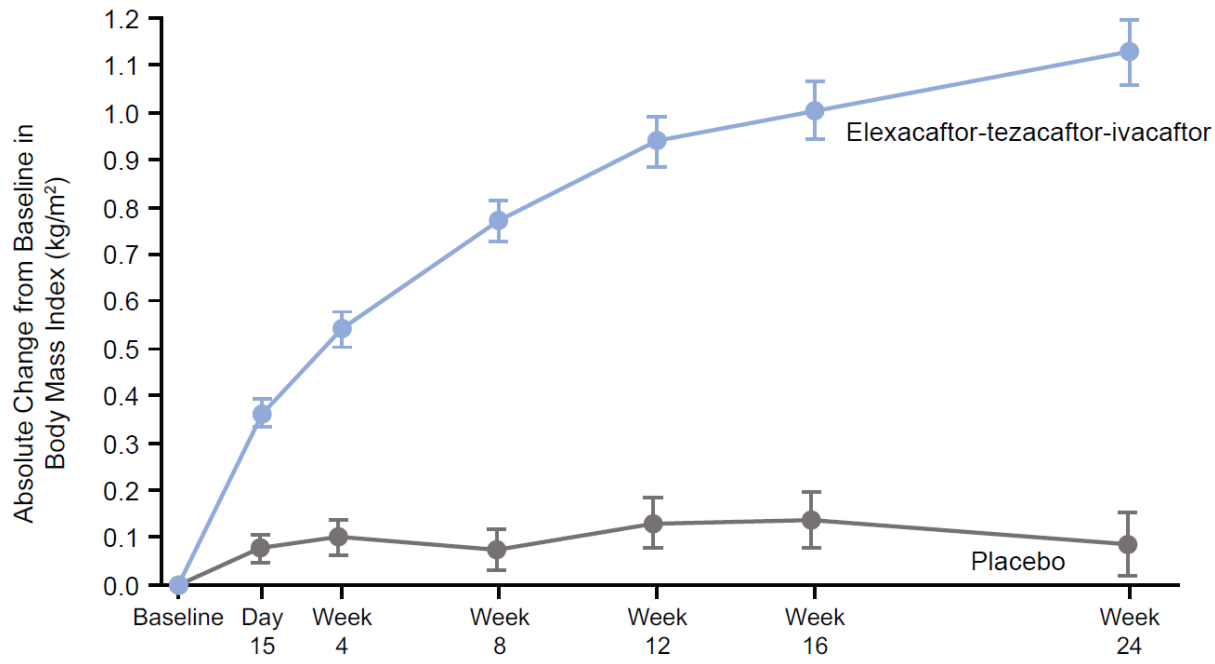
* Kaplan-Meier plot of time-to-first pulmonary exacerbation event is shown. Hazard ratio is based on Cox proportional hazard regression model.

Figure S5. Mean Sweat Chloride Concentration at Each Time Point.*



* Data are mean sweat chloride concentration at each time point shown, and error bars indicate standard error of the mean; the dotted line indicates the 60 mmol/liter diagnostic threshold for cystic fibrosis.

Figure S6. Absolute Change Over Time From Baseline in Body Mass Index.*



* Absolute change from baseline in the body mass index (the weight in kilograms divided by the square of the height in meters), based on a mixed-effects model for repeated measures. Data are least-squares means and error bars indicate standard error of the mean.

Supplementary Methods

Table S1. Qualifying Minimal Function Mutations Per Protocol

Minimal Function Mutation Category		**Mutation**				
Class I mutations (absence of CFTR protein production)	Nonsense mutations	Q2X	L218X	Q525X	R792X	E1104X
		S4X	Q220X	G542X	E822X	W1145X
		W19X	Y275X	G550X	W882X	R1158X
		G27X	C276X	Q552X	W846X	R1162X
		Q39X	Q290X	R553X	Y849X	S1196X
		W57X	G330X	E585X	R851X	W1204X
		E60X	W401X	G673X	Q890X	L1254X
		R75X	Q414X	Q685X	S912X	S1255X
		L88X	S434X	R709X	Y913X	W1282X
		E92X	S466X	K710X	Q1042X	Q1313X
		Q98X	S489X	Q715X	W1089X	Q1330X
		Y122X	Q493X	L732X	Y1092X	E1371X
		E193X	W496X	R764X	W1098X	Q1382X
		W216X	C524X	R785X	R1102X	Q1411X
	Canonical splice mutations	185+1G→T	711+5G→A	1717-8G→A	2622+1G→A	3121-1G→A
		296+1G→A	712-1G→T	1717-1G→A	2790-1G→C	3500-2A→G
		296+1G→T	1248+1G→A	1811+1G→C	3040G→C (G970R)	3600+2insT
		405+1G→A	1249-1G→A	1811+1.6kbA→G	3850-1G→A	
		405+3A→C	1341+1G→A	1811+1643G→T	3120G→A	4005+1G→A
		406-1G→A	1525-2A→G	1812-1G→A	3120+1G→A	4374+1G→T
		621+1G→T	1525-1G→A	1898+1G→A	3121-2A→G	
		711+1G→T	1898+1G→C			

	Small (≤3 nucleotide) insertion/deletion (ins/del) frameshift mutations	182delT	1078delT	1677delTA	2711delT	3737delA
		306insA	1119delA	1782delA	2732insA	3791delC
		306delTAGA	1138insG	1824delA	2869insG	3821delT
		365-366insT	1154insTC	1833delT	2896insAG	3876delA
		394delTT	1161delC	2043delG	2942insT	3878delG
		442delA	1213delT	2143delT	2957delT	3905insT
		444delA	1259insA	2183AA→G*	3007delG	4016insT
		457TAT→G	1288insTA	2184delA	3028delA	4021dupT
		541delC	1343delG	2184insA	3171delC	4022insT
		574delA	1471delA	2307insA	3171insC	4040delA
		663delT	1497delGG	2347delG	3271delGG	4279insA
		849delG	1548delG	2585delT	3349insT	4326delTC
		935delA	1609del CA	2594delGT	3659delC	
	Non-small (>3 nucleotide) insertion/deletion (ins/del) frameshift mutations	CFTRdele1	CFTRdele16-17b	1461ins4		
		CFTRdele2	CFTRdele17a,17b	1924del7		
		CFTRdele2,3	CFTRdele17a-18	2055del9→A		
		CFTRdele2-4	CFTRdele19	2105-2117del13insAGAAA		
		CFTRdele3-10,14b-16	CFTRdele19-21	2372del8		
		CFTRdele4-7	CFTRdele21	2721del11		
		CFTRdele4-11	CFTRdele22-24	2991del32		
		CFTR50kbdel	CFTRdele22,23	3121-977_3499+248del2515		
		CFTRdup6b-10	124del23bp	3667ins4		
		CFTRdele11	602del14	4010del4		
		CFTRdele13,14a	852del22	4209TGTT→AA		
		CFTRdele14b-17b	991del5			
Missense and in-frame deletion mutations	Missense mutations that are not responsive in vitro to tezacaftor, ivacaftor, or tezacaftor/ivacaftor	A46D†	V520F	Y569D†	N1303K	
		G85E	A559T†	L1065P		
		R347P	R560T	R1066C		
		L467P†	R560S	L1077P†		
		I507del	A561E	M1101K		

	and %PI >50% and sweat chloride >86 mmol/liter‡	

%PI: percentage of *F508del-CFTR* heterozygous patients in the CFTR2 patient registry who are pancreatic insufficient.[1]

* Also known as 2183delAA→G.

† Unpublished data.

‡ Mean sweat chloride of *F508del-CFTR* heterozygous patients in the CFTR2 patient registry.[1]

Supplementary Results

Table S2. Additional Clinical Characteristics at Baseline

	Placebo (N=203)	Elexacaftor-Tezacaftor-Ivacaftor (N=200)
Prior use of inhaled antibiotic — no. (%)*	132 (65.0)	118 (59.0)
Prior use of dornase alfa — no. (%)*	164 (80.8)	162 (81.0)
Prior use of inhaled bronchodilator — no. (%)*	191 (94.1)	187 (93.5)
Prior use of inhaled hypertonic saline — no. (%)*	127 (62.6)	147 (73.5)
Prior use of inhaled corticosteroids — no. (%)*	119 (58.6)	120 (60.0)
Prior use of azithromycin — no. (%)*	114 (56.2)	110 (55.0)
Pseudomonas aeruginosa positive within previous 2 years — no. (%)	142 (70.0)	150 (75.0)

* Includes medications administered during 56 days before the first dose of study drug.

Table S3. Absolute Change From Baseline in Percentage of Predicted FEV_1 at Week 4 by Genotype Subgroup*

	Placebo (N=203)	**Elexacaftor-Tezacaftor-Ivacaftor (N=200)**
Genotype subgroup: missense and in-frame deletions		
n†	38	44
Least-squares mean (95% CI) — percentage points	0.0 (-2.4 to 2.5)	11.3 (9.1 to 13.6)
Least-squares mean difference (95% CI)	11.3 (8.0 to 14.7)	
Genotype subgroup: class I (absence of CFTR protein production)		
n†	150	141
Least-squares mean (95% CI) — percentage points	-0.2(-1.5 to 1.1)	14.4 (13.0 to 15.7)
Least-squares mean difference (95% CI)	14.5 (12.6 to 16.4)	

* Ad hoc analysis of genotype subgroups was based on the characteristics of the minimal function allele. The other allele was always *F508del*. The least-squares mean difference between the elexacaftor-tezacaftor-ivacaftor group and the placebo group was based on a mixed-effects model for repeated measures.

† Sample size for number of patients with non-missing data at week 4.

Table S4. Absolute Change From Baseline in Percentage of Predicted FEV_1 at Week 4 in Patients With Percentage of Predicted FEV_1 <40 at Baseline*

	Placebo (N=16)	**Elexacaftor-Tezacaftor-Ivacaftor (N=18)**
n†	16	17
Least-squares mean (95% CI) — percentage points	0.8 (-4.9 to 6.5)	16.0 (10.6 to 21.4)
Difference (95% CI)	15.2 (7.3 to 23.1)	

* This analysis was ad hoc. The difference is the least-squares mean difference between the elexacaftor-tezacaftor-ivacaftor group and the placebo group on the basis of the mixed-effects model for repeated measures.

† Sample size for number of patients with non-missing data at week 4.

Table S5. Other Secondary Efficacy Endpoints

Endpoint	Placebo (N=203)	Elexacaftor-Tezacaftor-Ivacaftor (N=200)	Difference (95% CI)*
Time-to-first pulmonary exacerbation through week 24			
Kaplan-Meier probability of not having pulmonary exacerbation through 24 weeks (95% CI)	0.629 (0.558 to 0.692)	0.842 (0.783 to 0.886)	NA
Hazard ratio for pulmonary exacerbation through 24 weeks in elexacaftor-tezacaftor-ivacaftor group relative to placebo group	NA	NA	0.34 (0.22 to 0.52)
Absolute change from baseline in body mass index-for-age z score at week 24 — least-squares mean (95% CI)†	0.04 (-0.05 to 0.14)	0.34 (0.25 to 0.44)	0.30 (0.17 to 0.43)
Absolute change from baseline in body weight (kg) from baseline at week 24 — least-squares mean (95% CI)	0.5 (0.2 to 0.9)	3.4 (3.0 to 3.8)	2.9 (2.3 to 3.4)

NA, not applicable.

* The difference is the least-squares mean difference between the elexacaftor-tezacaftor-ivacaftor group and the placebo group based on a mixed-effects model for repeated measures, except for time-to-first pulmonary exacerbation, for which the

Kaplan-Meier estimate and hazard ratio based on a Cox proportional hazard regression model is shown.

† Data included only patients who were age 20 years or younger at baseline (74 patients in the placebo group and 71 in the elexacaftor-tezacaftor-ivacaftor group).

Table S6. Serious Adverse Events Occurring in ≥2 Patients in Either Treatment Group

	Placebo (N=201)	**Elexacaftor-Tezacaftor-Ivacaftor (N=202)**
	number of patients (percent)	
Overall number of patients with ≥1 serious adverse event	42 (20.9)	28 (13.9)
Infective pulmonary exacerbation of cystic fibrosis	33 (16.4)	11 (5.4)
Influenza	0	3 (1.5)
Rash events*	1 (0.5)	3 (1.5)
Hemoptysis	3 (1.5)	2 (1.0)

Adverse events were coded using MedDRA version 22.0. A patient with multiple events within a category was counted only once in that category.

* Group term of “rash events” includes terms of rash and rash pruritic.

Table S7. Summary of Rash Events*

	Placebo (N=201)	**Elexacaftor-Tezacaftor-Ivacaftor (N=202)**
	number of patients (percent)	
Overall number of patients with ≥1 rash event	13 (6.5)	22 (10.9)
Male	5/105 (4.8)	6/104 (5.8)
Female	8/96 (8.3)	16/98 (16.3)
Hormonal contraceptive use†	3/32 (9.4)	8/39 (20.5)
No hormonal contraceptive use	5/64 (7.8)	8/59 (13.6)

Rash events were coded using MedDRA version 22.0. When summarizing number and percent of patients, a patient with multiple events was counted only once.

* Group term of “rash events” includes terms of rash (e.g., rash, rash generalized, rash macular, rash pruritic).

† Hormonal contraceptive therapy included oral, topical, subcutaneous, intravaginal, and intrauterine routes of delivery, as well as estrogen replacement therapy.

Table S8. Summary of Adverse Events of Creatine Kinase Elevation

	Placebo (N=201)	**Elexacaftor-Tezacaftor-Ivacaftor (N=202)**
	number of patients (percent)	
Overall number of patients with ≥1 AE of creatine phosphokinase elevation†	9 (4.5)	20 (9.9)
AE of blood creatine phosphokinase increased	9 (4.5)	19 (9.4)
AE of rhabdomyolysis	1 (0.5)	2 (1.0)‡

AE, adverse event. Adverse events were coded using MedDRA version 22.0. A patient with multiple events within a category was counted only once in that category.

† These events were often associated with exercise, and none led to study drug discontinuation.

‡ These patients had creatine kinase increase without kidney involvement or myoglobinuria.

Table S9. Summary of Blood Pressure Data

	Placebo (N=201)	**Elexacaftor-Tezacaftor-Ivacaftor (N=202)**
Systolic blood pressure data		
Baseline*, mean mm Hg	113.7 (n=201)	113.4 (n=202)
Change from baseline*, mean mm Hg		
At week 4	-1.9 (n=199)	2.3 (n=201)
At week 12	0.4 (n=199)	3.5 (n=199)
At week 24	-0.1 (n=198)	3.1 (n=198)
Threshold analysis of patients with systolic blood pressure elevation on ≥2 occasions		
>140 mm Hg — n (%)	7 (3.5)	10 (5.0)
>140 mm Hg and >10 mm Hg increased from baseline* — n (%)	3 (1.5)	8 (4.0)
Diastolic blood pressure data		
Baseline*, mean mm Hg	69.7 (n=201)	69.4 (n=202)
Change from baseline*, mean mm Hg		
At week 4	-0.8 (n=199)	1.5 (n=201)
At week 12	-0.1 (n=199)	1.7 (n=199)

At week 24	0.3 (n=198)	1.9 (n=198)
Threshold analysis of patients with diastolic blood pressure elevation on ≥2 occasions		
>90 mm Hg — n (%)	7 (3.5)	6 (3.0)
>90 mm Hg and >5 mm Hg increased from baseline* — n (%)	4 (2.0)	3 (1.5)
Number of patients with ≥1 adverse event of blood pressure increased†	2 (1.0)	1 (0.5)

* Baseline is defined as the most recent non-missing measurement before the first dose of study drug in the treatment period.

† None of the adverse events of blood pressure increased were serious, and none led to study drug interruption or discontinuation.

Supplementary References

1. The Clinical and Functional Translation of CFTR. Variant List History. Accessed February 15, 2016 at: http://www.cftr2.org/.
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3. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40:1324-43.
4. Fuchs HJ, Borowitz DS, Christiansen DH, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. N Engl J Med 1994;331:637-42.

Data Sharing Statement

Vertex is committed to advancing medical science and improving patient health. This includes the responsible sharing of clinical trial data with qualified researchers. Proposals for the use of these data will be reviewed by a scientific board. Approvals are at the discretion of Vertex and will be dependent on the nature of the request, the merit of the research proposed, and the intended use of the data. Please contact CTDS@vrtx.com if you would like to submit a proposal or need more information.